**DOCKET NO.: ISIS-4682** 

Application No.: 09/775,967

Office Action Dated: December 2, 2003

This listing of claims will replace all prior versions, and listings, of claims in the application.

**Listing of Claims:** 

A method comprising reacting a nucleoside phosphoramidite with a support bound 1 (original).

oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one

unprotected internucleoside linkage selected from the group consisting of phosphate linkages,

phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an

aromatic heterocyclic amine, a guanidine, or a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a quaternary tetraalkylammonium cation, or a protonated form of

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an

aromatic heterocyclic amine, or a guanidine; and

E is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or

unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate

anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate

anion.

2 (original).

The method of claim 1 wherein said neutralizing agent is a salt of formula D<sup>+</sup>E<sup>-</sup>.

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The method of claim 2 wherein E is a tetrazolide anion. 3 (original).

The method of claim 1 wherein E is 1H-tetrazolide anion, 5-methylthio-1H-4 (original).

tetrazolide anion, 5-ethylthio-1H-tetrazolide anion or 1-phenyl-5-thiol-1H-tetrazolide anion.

The method of claim 1 wherein E is 1H-tetrazolide anion. 5 (original).

The method of claim 3 wherein D<sup>+</sup> is a protonated form of any of an alkyl, alkenyl 6 (original).

or alkynyl amine having from one to about 20 carbons, an aliphatic heterocyclic amine, an aromatic

heterocyclic amine, or a guanidine.

7-10 (canceled).

11 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a protonated form of an aromatic heterocyclic amine; and

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E is a tetrazolide anion.

A method comprising reacting a nucleoside phosphoramidite with 12 (previously presented).

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is a salt of formula D+E wherein:

D<sup>+</sup> is a protonated form of a mono-, di- or trialkyl pyridine that is

optionally substituted with an amino group; and

E is a tetrazolide anion.

13 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine,

2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-

butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine; and

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E is a tetrazolide anion.

14 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a protonated form of an alkylamino substituted pyridine; and

E is a tetrazolide anion.

15 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a protonated form of 4-dimethylaminopyridine; and

E is a tetrazolide anion.

16-20 (canceled).

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21 (original). The method of claim 3 wherein E is 1H-tetrazolide anion.

22-35 (canceled).

36 (previously presented). A method comprising reacting a nucleoside phosphoramidite with a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages; wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D+E- wherein:

D<sup>+</sup> is a protonated form of an aromatic heterocyclic amine; and

E<sup>-</sup> is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

37 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

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a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one unprotected internucleoside linkage selected from the group consisting of phosphate

wherein said neutralizing agent is:

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group; and

E<sup>-</sup> is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

38 (previously presented). A method comprising reacting a nucleoside phosphoramidite with a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one unprotected internucleoside linkage selected from the group consisting of phosphate linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an

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aromatic heterocyclic amine, a guanidine, or a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine; and

E<sup>-</sup> is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

39 (previously presented). A method comprising reacting a nucleoside phosphoramidite with a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having at least one unprotected internucleoside linkage selected from the group consisting of phosphate linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D+ is a protonated form of an alkylamino substituted pyridine; and

E<sup>-</sup> is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate

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anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate

anion.

40 (previously presented). A method comprising reacting a nucleoside phosphoramidite with

a support bound oligomer in the presence of a neutralizing agent, said support bound oligomer having

at least one unprotected internucleoside linkage selected from the group consisting of phosphate

linkages, phosphorothioate linkages, and phosphorodithioate linkages;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an

aromatic heterocyclic amine, a guanidine, or a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a protonated form of 4-dimethylaminopyridine; and

E is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or

unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate

anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate

anion.

41-46 (canceled).

47 (original). The method of claim 3 wherein D<sup>+</sup> is a protonated form of trimethyl amine,

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triethyl amine, triisopropyl amine, tributyl amine, triamyl amine, isopropyldimethyl amine, t-

butyldimethyl amine, diisopropylethyl amine, N,N,N',N'-tetramethyl-1,2-diaminoethane, DBU,

-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N'-dimethylpiperazine,

-ethylpyrrolidine, N-ethylpiperidine, N,N'-diethylpiperazine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-

diazabicyclo[2.2.2]octane, or 1,5,7-triazabicyclo[4.4.0]dec-5ene, 2,4,6-collidine, 2,6-lutidine, pyridine,

2-methylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-

tri(t-butyl)pyridine, 4-dimethylaminopyridine, or N,N,N'N'-tetramethylguanidine, or

tetramethylammonium, tetraethylammonium, tetrapropylammonium, tetrabutylammonium,

trimethyloctylammonium, or triethylbenzylammonium cation; and

E is 1H-tetrazolide anion, 4,5-dicyanoimidazolide anion, methylsulfonate anion,

trifluoromethylsulfonate anion, methylphenylsulfonate anion, trifluoromethylphenylsulfonate anion,

tetrafluoroborate anion, hexafluorophosphate anion, or trifluoroacetate anion.

48 (currently amended). A method of forming an internucleoside linkage comprising

reacting a phosphoramidite of formula:

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$$R_1$$
— $O$ 
 $R_2$ 
 $R_2$ 
 $R_2$ 
 $R_2$ 
 $R_2$ 
 $R_3$ 
 $R_4$ 
 $R_4$ 
 $R_5$ 
 $R_5$ 
 $R_7$ 
 $R_7$ 

### wherein:

L<sub>1</sub> is an internucleoside linkage;

 $n_1$  is 0 to about 100;

R<sub>1</sub> is a hydroxyl protecting group;

R<sub>2</sub> is a 2'-substituent group, said 2'-substituent group being fluoro, chloro, bromo, O-alkyl, O-alkylamino, O-alkylamino, O-alkylamino, O-alkylaminoalkyl, or alkylaminoalkyl, or alkylaminoalkyl, or alkylaminoalkyl, or alkylaminoalkyl, alkenyl, or alkylaminoalkyl, alkenyl, or alkylaminoalkyl, alkenyl, or alkylaminoalkyl, alkenyl, or alkylaminoalkyl, or alkylaminoalkyl, or alkylaminoalkyl, or alkylaminoalkyl, or alkylaminoalkyl, or alkylaminoalkyl, alkenyl, or alkylaminoalkyl, or alkylaminoa

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### wherein:

E is  $C_1$ - $C_{10}$  alkyl,  $N(R_{12})(R_{13})$  or  $N=C(R_{12})(R_{13})$ ;

each  $R_{12}$  and  $R_{13}$  is, independently, H,  $C_1$ - $C_{10}$  alkyl, a nitrogen protecting group, or  $R_{12}$  and  $R_{13}$ , together, are a nitrogen protecting group or are joined in a ring structure that includes at least one additional heteroatom selected from N and O;

 $R_{14}$  is  $OX_1$ ,  $SX_1$ , or  $N(X_1)_2$ ;

each  $X_1$  is, independently, H,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_8$  haloalkyl,  $C(=NH)N(H)Z_1$ ,  $C(=O)N(H)Z_1$  or  $OC(=O)N(H)Z_1$ :

 $Z_1$  is H or  $C_1$ - $C_8$  alkyl;

 $L_1$ ,  $L_2$  and  $L_3$  comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 heteroatoms, said heteroatoms being selected from oxygen, nitrogen and sulfur, wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

 $\underline{Y}_m$  is  $\underline{C}_1$ - $\underline{C}_{10}$  alkyl or haloalkyl,  $\underline{C}_2$ - $\underline{C}_{10}$  alkenyl,  $\underline{C}_2$ - $\underline{C}_{10}$  alkynyl,  $\underline{C}_6$ - $\underline{C}_{14}$  aryl,  $\underline{N}(\underline{R}_{12})(\underline{R}_{13})$   $\underline{OR}_{12}$ , halo,  $\underline{SR}_{12}$  or  $\underline{CN}$ ;

each q<sub>1</sub> is, independently, an integer from 2 to 10;

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each  $q_2$  is 0 or 1;

p is an integer from 1 to 10; and

q<sub>3</sub> is an integer from 1 to 10;

provided that when p is 0, q<sub>3</sub> is greater than 1;

B is a nucleobase;

Q is O or S;

Pg is a phosphoryl protecting group;

# with a compound of formula:

HO
$$R_2$$
 $R_3$ 
 $R_3$ 
 $R_2$ 

# wherein

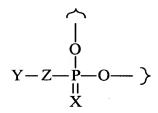
R<sub>3</sub> is a linker connected to a solid support;

n is from 1 to 100; and

L is an internucleoside linkage of formula:

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#### wherein:

Z is O or S;

X is O or S; and

Y is a phosphoryl protecting group or a negative charge;

provided that at least one Y is a negative charge;

wherein said reaction is performed in the presence of a neutralizing agent;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

49 (original). The method of claim 48 wherein said neutralizing agent is a salt of formula  $D^+$   $E^-$ .

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50 (original). The method of claim 49 wherein E is a tetrazolide anion.

51 (original). The method of claim 48 wherein E<sup>-</sup> is 1H-tetrazolide anion, 5-methylthio-1H-tetrazolide anion, 5-ethylthio-1H-tetrazolide anion or 1-phenyl-5-thiol-1H-tetrazolide anion.

52 (original). The method of claim 48 wherein E is 1H-tetrazolide anion.

53-55 (canceled).

56 (original). The method of claim 50 wherein D<sup>+</sup> is a protonated form of an aromatic heterocyclic amine.

57 (original). The method of claim 50 wherein D<sup>+</sup> is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group.

58 (original). The method of claim 50 wherein D<sup>+</sup> is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine.

59 (original). The method of claim 50 wherein D<sup>+</sup> is a protonated form of an alkylamino substituted pyridine.

60 (original). The method of claim 50 wherein D<sup>+</sup> is a protonated form of 4-dimethylaminopyridine.

61-65 (canceled).

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66 (original). The method of claim 50 wherein E is 1H-tetrazolide anion.

67-80 (canceled).

81 (original). The method of claim 48 wherein D<sup>+</sup> is a protonated form of an aromatic heterocyclic amine.

82 (original). The method of claim 48 wherein D<sup>+</sup> is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group.

83 (original). The method of claim 48 wherein D<sup>+</sup> is a protonated form of any of 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-diethylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine.

84 (original). The method of claim 48 wherein D<sup>+</sup> is a protonated form of an alkylamino substituted pyridine.

85 (original). The method of claim 48 wherein  $D^+$  is a protonated form of 4-dimethylaminopyridine.

86-91 (canceled).

92 (original). The method of claim 50 wherein D<sup>+</sup> is a protonated form of trimethyl amine, triethyl amine, triisopropyl amine, tributyl amine, triamyl amine, isopropyldimethyl amine, t-butyldimethyl amine, diisopropylethyl amine, N,N,N',N'-tetramethyl-1,2-diaminoethane, DBU, N-

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methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N'-dimethylpiperazine, N-ethylpyrrolidine, N-ethylpiperidine, N,N'-diethylpiperazine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, or 1,5,7-triazabicyclo[4.4.0]dec-5ene, 2,4,6-collidine, 2,6-lutidine, pyridine, 2-methylpyridine, 2,6-di(t-butyl)pyridine, 4-methyl-2,6-di(t-butyl)pyridine, or 2,4,6-tri(t-butyl)pyridine, 4-dimethylaminopyridine, or N,N,N'N'-tetramethylguanidine, or tetramethylammonium, tetraethylammonium, tetraethylammonium, tetrabutylammonium, trimethyloctylammonium, or triethylbenzylammonium cation; and

E is 1H-tetrazolide anion, 4,5-dicyanoimidazolide anion, methylsulfonate anion, trifluoromethylsulfonate anion, methylphenylsulfonate anion, trifluoromethylphenylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or trifluoroacetate anion.

93 (original). The method of claim 50 wherein Q is O; Z is O;

Pg is  $\beta$ -cyanoethyl, methyl, (N-methyl-N-benzoylamino)ethyl, (N-ethyl-N-benzoylamino)ethyl, 2-[N-methyl-N-(4-methoxybenzoyl)amino]ethyl, 2-(N-isopropyl-N-benzoylamino)ethyl, 2-[N-ethyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-methyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-ethyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-(thionobenzoylamino)ethyl, 3-(thionobenzoyl-amino)propyl, 2-(N-phenylthiocarbamoylamino)ethyl, 2-[(1-naphthyl)carbamoyloxy]ethyl, diphenyl-silylethyl,  $\delta$ -cyanobutenyl, cyano p-xylyl, methyl-N-trifluoroacetyl ethyl or acetoxy phenoxy ethyl; and

Y is  $\beta$ -cyanoethyl, allyl, methyl, (N-methyl-N-benzoylamino)ethyl, (N-ethyl-N-benzoylamino)ethyl, 2-[N-methyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-isopropyl-N-benzoylamino)ethyl, 2-[N-ethyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-methoxybenzoyl)amino]ethyl, 2-[N-methyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-ethyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-[N-isopropyl-N-(4-dimethylaminobenzoyl)amino]ethyl, 2-(thionobenzoylamino)ethyl, 2-(N-phenylthiocarbamoylamino)ethyl, 2-[(1-naphthyl)carbamoyloxy]ethyl, diphenylsilylethyl,  $\delta$ -cyanobutenyl, cyano p-xylyl, methyl-N-

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trifluoroacetyl ethyl, acetoxy phenoxy ethyl, or a negative charge.

94 (original). The method of claim 48 wherein:

said neutralizing agent is a salt of formula D+E-;

E is a tetrazolide anion:

D<sup>+</sup> is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group;

Q is O;

Z is O;

 $R_4$  and  $R_5$  are each diisopropyl, or  $R_4$  and  $R_5$  together with the nitrogen atom to which they are attached form morpholine;

Pg is  $\beta$ -cyanoethyl, methyl, diphenylsilylethyl,  $\delta$ -cyanobutenyl, cyano p-xylyl, methyl-N-trifluoroacetyl ethyl or acetoxy phenoxy ethyl; and

Y is  $\beta$ -cyanoethyl, allyl, methyl, diphenylsilylethyl,  $\delta$ -cyanobutenyl, cyano p-xylyl, methyl-N-trifluoroacetyl ethyl or acetoxy phenoxy ethyl or a negative charge.

95 (original). The method of claim 94 wherein:

E is 1H-tetrazolide anion;

D<sup>+</sup> is a protonated form of dimethylaminopyridine;

Pg is  $\beta$ -cyanoethyl, diphenylsilylethyl,  $\delta$ -cyanobutenyl, cyanop-xylyl, methyl-N-trifluoroacetyl ethyl or acetoxy phenoxy ethyl; and

Y is  $\beta$ -cyanoethyl, allyl, diphenylsilylethyl,  $\delta$ -cyanobutenyl, cyano p-xylyl, methyl-N-trifluoroacetyl ethyl, acetoxy phenoxy ethyl or a negative charge.

96 (original). A method comprising the steps of:

(a) providing a solid support having a 5'-O-protected phosphorus-linked oligomer bound

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thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that does not bear a phosphoryl protecting group;

- (b) deprotecting the 5'-hydroxyl of the 5'-O-protected phosphorus-linked oligomer with a deprotecting reagent;
- (c) washing the deprotected phosphorus-linked oligomer on the solid support with a solution containing a neutralizing agent;
- (d) reacting the deprotected 5'-hydroxyl with an 5'-protected nucleoside phosphoramidite to produce a phosphite triester linkage therebetween; and
- (e) oxidizing or sulfurizing the covalent linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage; and

optionally repeating steps b through e at least once for subsequent couplings of additional nucleoside phosphoramidites;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E<sup>-</sup> is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

# 97 (original). A method comprising the steps of:

(a) providing a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that

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does not bear a phosphoryl protecting group;

(b) deprotecting the 5'-hydroxyl of the 5'-O-protected phosphorus-linked oligomer with a deprotecting reagent to form a support bound 5'-deprotected phosphorus-linked oligomer;

- (c) optionally washing the deprotected phosphorus-linked oligomer on the solid support;
- (d) contacting the support bound 5'-deprotected phosphorus-linked oligomer with a solution comprising a 5'-protected nucleoside phosphoramidite to produce a phosphite triester linkage therebetween, wherein said solution further comprises a neutralizing agent; and
- (e) oxidizing or sulfurizing the phosphite triester linkage to form a phosphodiester, phosphorodithioate or H-phosphonate linkage; and

optionally repeating steps b through e at least once for subsequent couplings of additional nucleoside phosphoramidites;

wherein said neutralizing agent is:

an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E<sup>-</sup> is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

98 (previously presented). A composition comprising a 5'-protected nucleoside phosphoramidite and a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

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E<sup>-</sup> is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion.

99 (previously presented). A composition comprising a 5'-protected nucleoside phosphoramidite and a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

E- is a tetrazolide anion; and

D<sup>+</sup> is a protonated form of a mono-, di- or trialkyl pyridine that is optionally substituted with an amino group.

100 (previously presented). A composition comprising a 5'-protected nucleoside phosphoramidite and a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

E is 1H-tetrazolide anion; and

D<sup>+</sup> is a protonated form of dimethylaminopyridine.

101 (previously presented). A composition comprising:

- -- a 5'-protected nucleoside phosphoramidite;
- -- a salt of formula D<sup>+</sup>E<sup>-</sup> wherein:

D<sup>+</sup> is a quaternary tetraalkylammonium cation, or a protonated form of an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, or a guanidine; and

E is a tetrazolide anion, 4,5-dicyanoimidazolide anion, a substituted or unsubstituted alkylsulfonate anion, a substituted or unsubstituted arylsulfonate anion, tetrafluoroborate anion, hexafluorophosphate anion, or a trihaloacetate anion; and

-- a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that does

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not bear a phosphoryl protecting group.

102 (canceled)

103 (original). The composition of claim 100 further comprising a solid support having a 5'-O-protected phosphorus-linked oligomer bound thereto, said phosphorus-linked oligomer having at least one phosphoryl internucleoside linkage that does not bear a phosphoryl protecting group.

104. (previously presented) The method of claim 50 wherein D+ is a protonated form of alkyl, alkenyl or alkynyl amine having from one to about 20 carbons, an aliphatic heterocyclic amine, an aromatic heterocyclic amine, or a guanidine.

105. (Canceled)